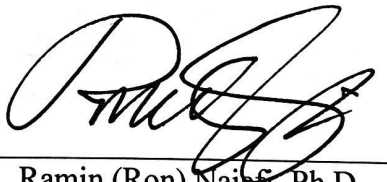
EXHIBIT 4

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 2875** **Civil NO. 19-02875 (RBK/JS)**

EXPERT REPORT OF
RAMIN (RON) NAJAFI, Ph.D.

Date: October 31, 2022



Ramin (Ron) Najafi, Ph.D.

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QUALIFICATIONS

I received my B.S. and M.S. in Organic Chemistry from the University of San Francisco in June of 1983. During my time at the University of San Francisco, I held a position as a Teaching Assistant for Organic Chemistry Lab from 1982 to 1983. While studying at the University, I authored "The Hydroboration of Alkenyl Metalloids", which I presented at the 32nd Annual ACS Northern California Regional Undergraduate Research Conference, and "Selective Oxidation of Organoboranes with Anhydrous Trimethylamine *N*-Oxide" which was presented at the 185th National Meeting of the American Chemical Society in Seattle, Washington, and the 8th ACS Senior Technical Meeting at the University of San Francisco. I was the recipient of the University of San Francisco Student Affiliates of the American Chemical Society Award for Outstanding Achievement in Chemistry.

In December of 1988, I received my Ph.D. in Organic Chemistry from the University of California, Davis. While earning my doctorate degree, I worked as an Associate-Instructor and Teaching Assistant for Advanced Organic Synthesis and supervised undergraduate students in general and organic chemistry labs from 1983 to 1988. While studying at the University of California, I authored "Stereoselective Syntheses of Alkenyl-Substituted 1,3-Dioxolanes or 4,7-Dihydro-1,3 dioxepins or an (E)- α,β -Unsaturated Aldehyde from (Z)-2-Butene-1,4-diols" in the Journal of Organic Chemistry in 1985. In 1987, I was the recipient of the University of California, Dow Chemical Company Graduate Teaching Assistant Award in Recognition of Outstanding Graduate Accomplishments. In 1988, I published "Hydroboration of Methoxyenynes. A Novel Synthesis of (E)-Methoxyenones" in Tetrahedron Letters. Also, the year of my graduation, I was the recipient of the University of California Campus-Wide Teaching Award for Outstanding Graduate Students.

I have been a member of the American Chemical Society since 1979 as well as an Associate Member of Sigma Xi, a National Scientific Honor Society, since 1988. From 1993 to 1994, I was the Secretary of the Philadelphia Organic Chemist Club. I am also the Co-Founder of Vision in Chemistry Annual Symposium at Rhone Poulenc Rorer (now Sanofi-Aventis) from 1991 to present day. To date, I have authored over 20 publications relating to the study of chemistry and hold over 70 patents and pending patent applications on novel inventions.

In addition to my academic positions, I have held several scientific roles at companies such as Rhone Poulenc Rorer (now Sanofi-Aventis), Applied Biosystems – a division of Perkin Elmer (now Thermo Fisher), and Aldrich Chemical Company (now Millipore Sigma). These roles helped me develop extensive experience in all aspects of pharmaceutical and chemical development, spanning from the R&D stage to pilot plant manufacturing and beyond.

My work surrounding in the field of chemistry has been widely recognized by those in the scientific community when I was the recipient of Perkin-Elmer/Applied Biosystems President's Award for Innovative Discoveries in Chemistry amongst 1300 PhD's in 1995.

I have also been an entrepreneur founding three companies. From 1996 to 2002, I was President and CEO of CP Lab Safety, a company focused on environmental laboratory safety. In 2007, CP Lab Safety was the recipient of the Congressional Certificate of Environmental Sustainability from

Congressman Jared Huffman. In 2000, I founded NovaBay Pharmaceuticals, Inc., a pharmaceutical company centered on developing non-antibiotic antimicrobial therapies. In 2008, I took the company public and continued to serve as the President and CEO until 2015. In 2007, I was named Biotech Entrepreneur of the year by East Bay Business Journal. In 2011, I founded Najafi Pharma Inc., dba Emery Pharma, where I currently serve as Chairman and CEO. Our mission is to help Save Lives and Save the Environment.

Emery Pharma is a FDA registered and inspected, cGMP / GLP compliant Contract Research Laboratory which allows our team of Ph.D. Chemists and Biologists to assist pharmaceutical companies develop drugs following stringent regulatory guidance (FDA, ICH, USP, etc.). In addition to performing cGMP / GLP compliant work, Emery performs research and development work for pharmaceutical and technology companies.

As a chemist working in the pharmaceutical industry for 30 years, I have had to learn and become familiar with the regulatory requirements of the FDA governing the pharmaceutical industry including with respect to the development, testing, approval and manufacture of pharmaceuticals in the United States.

A true and correct copy of my Curriculum Vitae is provided as Exhibit "A" to this report that includes all publications on which I am listed as an author. My rate of compensation is $720 per hour. I have testified twice over the last four years. Both were depositions, one in this matter and one in the matter of In Re: Zantac (Ranitidine) Products Liability Litigation, Civil Action No. 9:20-md-2924, Southern District of Florida.

When forming my opinions, I employed methodologies used in the field of organic and analytical chemistry in the pharmaceutical industry, and by me in my own work, including testing, validation, risk assessment, risk management, and investigating the root cause of contamination or an impurity in a drug product. My opinions are based upon my education, practice, and experience, weighing the evidence, and on accepted practices in the field of chemistry and pharmaceutical industry, FDA guidance and regulations as well as industry standards and peer reviewed scientific literature.

My experience comes from 30 years of industry experience, first as a development chemist at Aldrich Chemical Company where I had hands-on experience in cGMP synthesis of various precursors of Active Pharmaceutical Ingredients (API). Later at Rhone Poulenc Rorer Pharmaceutical (now Sanofi Aventis), I worked as a Process Chemist who scaled up pharmaceutically active compounds into Pilot Plant and later into a manufacturing facility which involved awareness of the synthetic pathway and evaluation of many of the possible side reactions and potential impurities. Next, at Applied Biosystems, I was given a task of determining why a DNA (a 20mer) synthesis was only 90% pure and contained a large amount of unknown impurity. I was tasked to conduct a thorough root-cause analysis and find out the cause of the impurity. I was able to successfully discover a unique impurity in one of the key monomer components that was responsible for much of the impurity. For this discovery, I was recognized with The Perkin-Elmer/Applied Biosystems President's Award for Innovative Discoveries in Chemistry amongst 1300 PhD's in 1995.

In 1996, I left Applied Biosystems to form NovaBay Pharmaceuticals centered on my discovery of pure Hypochlorous Acid and NVC-422. In 2007, I took the company public and conducted multiple clinical trials in wound care, ophthalmology, common cold, impetigo, etc. around the globe. In the process, I used various contract manufacturers to manufacture our medicine under cGMP and used the finished product to conduct multiple clinical trials under an FDA approved IND (Investigational New Drug application). In 2011 and 2014, we brought two products to market: NeutroPhase for wound care and Avenova for blepharitis. I oversaw extensive stability studies where we also conducted shipping studies and elevated temperature studies (accelerated stability study) to evaluate the viability of our drug substance and drug product and which was submitted to the FDA as part of our approval.

The opinions I provide in this report are all expressed with a reasonable degree of scientific certainty.

SOURCES OF NITROSAMINE CONTAMINATION IN GENERAL

There can be many causes of nitrosamine impurities such as NDMA and NDEA in valsartan drug substance. They can form during the drug substance synthetic process or be present in the starting materials. They can result from intermediates that are not purged in later steps of the drug substance synthetic process. Recovered solvents and catalysts may be the source of nitrosamine contamination due to the presence of secondary or tertiary amines in the recovered compound and the subsequent quenching of these materials with nitrous acid to destroy residual azide which is not adequately removed. If solvents/catalysts are co-mingled, nitrosamine contamination can occur. Similarly, if adequate cleaning of equipment between different drug substance or products is not performed with shared use of equipment, nitrosamine contamination can occur.

Drug substance manufacturers are required to evaluate each synthetic process for its potential to form nitrosamine impurities. If there is a risk of forming nitrosamines, changes should be made to prevent in-situ forming nitrosamines. Drug substance (API) manufacturers should demonstrate their process is not at risk for forming impurities like the nitrosamines, NDMA and NDEA, in accordance with *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients Guidance for Industry*. See https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf. To do this, drug substance manufacturers should confirm and demonstrate through testing that their starting materials and any intermediates including raw materials such as recovered solvents and catalysts do not contain nitrosamines.

If the process cannot be modified to stop nitrosamines from forming, then a purification or elimination step should be added along with testing to verify the step was successful, and nitrosamines do not remain. See Q7 *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*, https://www.fda.gov/files/drugs/published/Q7-Good-Manufacturing-Practice-Guidance-for-Active-Pharmaceutical-Ingredients-Guidance-for-Industry.pdf; See Q11 *Development and Manufacture of Drug Substances*; https://www.fda.gov/media/80909/download. This testing should remain part of the process to ensure that nitrosamines are appropriately removed from the intermediate or finished drug substance so the drug product is as approved.

DIOVAN, AS THE APPROVED REFERENCED LISTED DRUG

Diovan, developed and manufactured by Novartis to treat high blood pressure or heart failure, was the brand name/innovator drug of generic valsartan. Diovan was also sold in finished doses that contained HCTZ (Diovan HCTZ) and under the brand name of Exforge and Exforge HCTZ if the finished dose also contained amlodipine. The New Drug Application (NDA) 021283 filed with the FDA by Novartis was approved in 2001. See https://www.accessdata.fda.gov/scripts/cder/daf/indeX.cfm?event=overview.process&ApplNo=021283. The approved formulation of Diovan is the drug to which generic versions are compared to show that they are therapeutically, pharmaceutically and bioequivalent. This is also known as the Referenced Listed Drug (RLD). When a drug company seeks authorization from the FDA to manufacture a generic drug, it must reference a RLD, and for generic valsartan, the RLD is Diovan.

The United States Pharmacopeia (USP) is an independent, scientific nonprofit organization that establishes quality standards for medicines including drug substances [also known as active pharmaceutical ingredients (APIs)] and excipients (inactive ingredients). The USP is an official quality standard for medicines sold in the United States. The monograph for valsartan articulates the quality expectations for "its identity, strength, purity, and performance." See https://www.usp.org/about/public-policy/overview-of-monographs. NDMA and NDEA are not approved as part of the standard.

Importantly, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the FDA have recognized the importance of risk assessment of the mutagenic potential of impurities, and the need to recognize and identify potential mutagenic impurities in drug substances and products. Both have provided guidance with a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk. See https://www.fda.gov/media/85885/download. Mutagenic impurities, like NDMA and NDEA, are DNA reactive substances that have a potential to directly cause DNA damage when present at low levels which can lead to mutations causing cancer. N-nitroso compounds like NDMA and NDEA are specifically recognized in the guidance as in the group of high potency mutagenic carcinogens known as the "cohort of concern." Guidance, page 5. Because NDMA and NDEA are highly potent mutagenic carcinogens, they must be eliminated, and if they cannot be eliminated must be tightly controlled at very low levels which are much lower than the impurity acceptance levels listed on the USP Monograph for the listed impurities or any other individual impurities. NDMA and NDEA are not listed on the US Monograph for valsartan as they are not an expected or accepted part of the approved formulation of valsartan. Additionally, the USP recognizes that "**nonmonograph tests and acceptance criteria suitable for detecting and controlling impurities that may result from a change in processing methods** or that may be introduced from external sources should be employed in addition to the tests provided on the individual monograph, where the presence of the impurity is inconsistent with applicable good manufacturing practices or good pharmaceutical practice." See USP 38, General Notices and Requirements, Section 5.60. Emphasis added. This section recognizes the need for testing for mutagenic impurities like NDMA and NDEA especially when a proper risk assessment of the manufacturing process is predicative of possible nitrosamine formation.

VALSARTAN CONTAINING PRODUCTS - FDA RECALL

The Food and Drug Administration in July of 2018 instituted a voluntary recall of several medicines containing valsartan following detection of the impurity, N-nitrosodimethylamine (NDMA). This recall occurred following a notification by API manufacturer Zhejiang Huahai Pharmaceuticals (ZHP) that NDMA was present in its drug substance.

In May of that year, Novartis, a customer of ZHP API, performed testing on the ZHP valsartan API (drug substance) as part of its qualification process. The residual solvent testing performed by gas chromatography revealed unidentified peaks indicating there may be an unwanted/unapproved chemical contaminant in the drug substance. ZHP confirmed that they found similar unidentified peaks in their testing of the same batches. ZHP00389304, 309. ZHP was subsequently notified by Novartis that the unidentified peaks were NDMA. ZHP00388642. The following pharmaceutical companies were subject to the recall because they used ZHP valsartan API in their finished drug products: Solco/Prinston, Torrent Pharma, Inc., and Teva Pharmaceutical Industries, Ltd.

Subsequently, on September 13, 2018, the FDA announced the discovery of another nitrosamine in ZHP valsartan drug products, N-nitrosodiethylamine (NDEA). Additional recalls were instituted. There were approximately 1,159 recalled angiotensin II receptor blockers (ARB) in all. A full list of the recalled ARB may be found at https://www.fda.gov/drugs/drug-safety-and-availability/search-list-recalled-angiotensin-ii-receptor-blockers-arbs-including-valsartan-losartan-and.

The FDA advised it had established interim limits of 96 ng per day (0.3 ppm) for NDMA and 26.5 ng for NDEA (0.083 ppm) so manufacturers could voluntarily recall their products if laboratory testing confirmed the presence of nitrosamine impurities above these levels. The FDA advised that it was working with industry and international regulators to ensure products entering the market did not contain these impurities but tolerated the impurities below the established level to avoid a possible shortage of ARBs. Update 2/28/2019 at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan. These limits have continued on an ongoing basis.

The FDA published laboratory test results for NDMA and NDEA in valsartan in May of 2019. The NDMA levels reported in the tested Prinston Pharmaceutical tablets containing 320 mg of valsartan ranged from 13.18 to 20.19 micrograms (13,180 to 20,190 nanograms) with NDEA below the limit of detection. NDMA found in Teva Pharmaceuticals tablets containing 320 mg of valsartan ranged from below the limit of detection in 11 lots tested, and 6.94 to 16.55 micrograms (6,940 to 16, 550 nanograms) in 5 lots tested with NDEA levels from below the limit of detection to 0.03 micrograms. The Torrent 320 mg valsartan tablets had between 0.56 to 0.62 micrograms (560 to 620 nanograms) of NDMA with 1.12 to 1.22 micrograms (1,120 to 1,220 nanograms) of NDEA from two of the lots tested while three other lots had 10.24 to 11.53 micrograms (10,240 to 11,530 nanograms) of NDMA with below the limit of detection for NDEA. One lot of 160 mg tablets had 0.45 micrograms (450 nanograms) of NDMA but 1.31 micrograms (1,310 nanograms) of NDEA. All of the ZHP drug products contained unacceptable levels of NDMA and/or NDEA.

Notably, the FDA identified 40 ARB medications where their assessment concluded that they did not contain any known nitrosamine impurities. The valsartan products that were not recalled in the United States included name-brand Diovan and Exforge (containing Valsartan) manufactured by Novartis Pharmaceuticals. See FDA Valsartan products not currently recalled – Updated September 21, 2018**.** Health Canada also tested name-brand Diovan and found no NDMA or NDEA. See Government of Canada: Impurities found in certain angiotensin II receptor blocker (ARB) products, also known as sartans at https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/angiotensin-receptor-blocker.html.

LEVELS OF NDMA AND NDEA IN VALSARTAN DRUG SUBSTANCE/VALSARTAN CONTAINING DRUGS

ZHP determined that the levels of NDMA measured in the valsartan API would carry over to the finished drug product. ZHP reached this determination by testing some batches of API and the corresponding final drug product to ascertain the impurity relationship. ZHP00683571, 00683578. By conducting this testing, ZHP found that the level of NDMA in the API and NDMA in the finished dose was almost the same. This was affirmed by the testimony of several ZHP witnesses including the President of Solco, Hai Wang, and ZHP's Director of Finished Dose Formulation Quality, Minli Zhang. Both agreed that the API and finished drug product had approximately the same levels of nitrosamines. Hai Wang Dep. Tr., 116:3-118:23, 144:15-147:1 – 3.10.2021; Minli Zhang Dep. Tr., 509:15-17, 518:18-519:3 – 3.26.2021. This was also reported to the FDA in filings that contained the statement that "it is confirmed that NDMA has been present in Valsartan drug substance (API) batches and carried to the drug product Valsartan." PRINSTON00249966, 249967; ZHP00099424, 99441-42. ZHP concluded this carry-over principle applied to NDEA as well. PRINSTON0075797, 75977 stating: "NDEA impurities, which is carried over into crude products, and finally remain in valsartan finished products." Teva's witness also testified that the levels of NDMA in their finished dose drug product would be the same as the levels in the API. Daniel Barreto Dep. Tr., 201:10 to 202:14, 275:24 to 276:5, 367:9 to 368:2. The presence of NDMA and/or NDEA in the drug substance at similar levels as present in the finished dose is because the NDMA and NDEA forms during the synthesis process, not the result of degradation of the valsartan molecule, which is consistent with Health Canada's test results finding no NDMA in Diovan.

The levels of NDMA and NDEA found by ZHP when testing their API were more than the acceptable daily intake limits established by the FDA for all batches sold in the United States. Hai Wang Dep. Tr. at 93:10-16, 154:5-11. The NDMA levels measured by ZHP reached 188.1 ppm which would result in over 60,000 nanograms for a single 320 mg valsartan tablet. ZHP00079913 at 79920-28. The NDEA levels measured by ZHP reached as high as 42.14 ppm which would result in over 13,000 nanograms for a 320 mg valsartan tablet. PRINSTON0075797 at 75858. Of note, these levels far exceed the acceptable daily intake levels of 0.3 ppm for NDMA and 0.083 ppm for NDEA established by the FDA. See https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan. ZHP API was in finished dose product of Huahai US/Solco/Prinston, Teva and Torrent with ANDAs filed by the finish dose drug product manufacturers. See Solco Healthcare US, LLC (ANDA 204821); Prinston Inc. (ANDA 206083), Teva Pharmaceutical Industries

Ltd/Watson Labs/Olm Labs (ANDA 077530; ANDA 090642; ANDA 091235; ANDA 091519; ANDA 200435) and Torrent (ANDA 202377; ANDA 202728)

ZHP manufactured valsartan API which was sold to Torrent, a finished dose manufacturer. The ZHP API manufactured sold to Torrent was made using the TEA process. Sushil Jaiswal, Dep. Tr. at 94-95. All valsartan API batches sold by ZHP to Torrent contained NDMA. ZHP02563814; Neravetla Dep. Tr. at 54-57. The levels of NDMA ranged from 0.37 to 125.15 ppm. TORRENT-MDL2875-00366178. NDEA levels ranged from 0.23 ppm to 16.93 ppm. TORRENT-MDL2875-00135398.

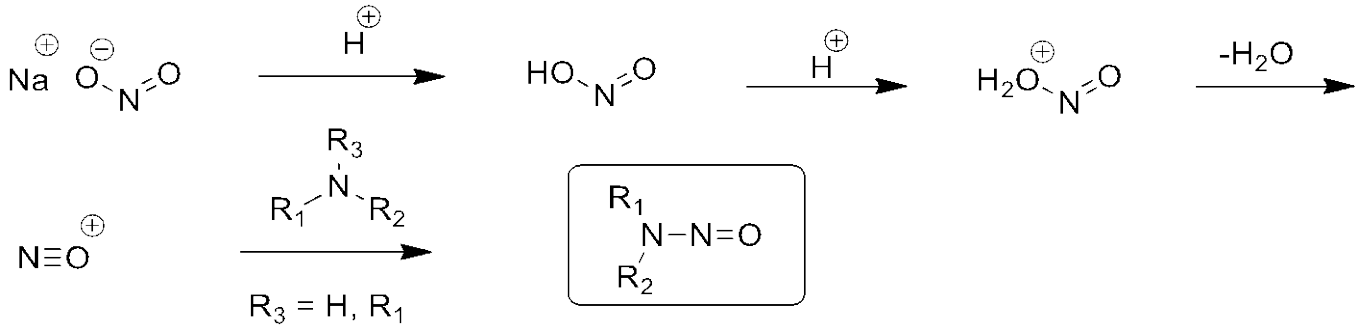
ZHP also manufactured valsartan API which was sold to Teva, a finished dose manufacturer. Teva Dep. Ex. 230. The ZHP API sold to Teva was manufactured using either the TEA process or the ZnCl2 process. TEVA-MDL2875-00950663, page 2. The valsartan API batches that ZHP sold to Teva all had NDMA contamination. The NDMA levels reported for Teva batches were between 0.8ppm and 240.1ppm. TEVA-MDL2875-00546489; TEVA-MDL2875-00549883. The NDEA levels reported were between less than the LOQ and 30.76 ppm. TEVA-MDL-00068938; TEVA-MDL2875-00701543.

NITROSAMINES – BACKGROUND INFORMATION

Both NDMA and NDEA are nitrosamines. Nitrosamines are not new, nor an unexpected impurity. The existence of such compounds and their potential toxicity has been well known since the 1970s. Further, the link between nitrate/nitrites and nitrosamine formation, as well as their effects on human health, have been discussed widely in the scientific literature dating back before the development of the ZHP manufacturing processes using sodium nitrite.

Nitrosamines are simple organic compounds that include a nitroso group (NO+) bonded to a nitrogen. These compounds are a class of chemical compounds with the general structures R_1R_2N-N=O. Nitrosamines can form from secondary and tertiary amines by a relatively simple chemical reaction which has been known for many years. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 17, Some N-nitroso compounds, pp 83-175, Lyon, France (1978).* Basic chemistry principles instruct us that secondary amine in the presence of nitrite and acid predictably and readily react to produce genotoxic nitrosamines such as NDMA and NDEA.

Below is a chemical schematic showing nitrosamine being generated by reaction of secondary amines with nitrite in acidic conditions:



Production of nitrosamines during a drug synthesis process is concerning because nitrosamines are part of the group of high potency mutagenic carcinogens referred to as the "cohort of concern" and are classified as Class I impurities. See *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), version May 2015, version March 2018*, https://www.fda.gov/media/85885/download; *ICH guideline M7(R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk*, August 25, 2015, https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-m7r1-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit_en.pdf.
Earlier FDA draft guidance also referenced that impurities with structural alerts such as compounds containing N-nitroso groups like NDMA and NDEA have extremely high carcinogenic potency. This draft guidance advised that such impurities should be identified, and attempts should be made to prevent their formation by considering alternate synthetic pathways. See also *Draft Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches, December 2008, Pharmacology and Toxicology, http://www.triphasepharmasolutions.com/Resources/Guidance%20for%20Industry%20Genotoxic%20Agents.pdf*. Similarly, the earlier 2007 EMA Guideline on the Limits of Genotoxic Impurities also recognized the N-nitroso compounds as a group of high potency genotoxic carcinogens. *EMA Guideline on the Limits of Genotoxic Impurities*, January 2007-January 2018, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-limits-genotoxic-impurities_en.pdf.

ESTABLISHMENT OF ACCEPTABLE DAILY INTAKE (ADI) OF NDMA AND NDEA

On February 28, 2019, the FDA published an updated table of interim acceptable intake limits for three nitrosamine impurities. This table sets forth the FDA ADI values for valsartan containing medications:

Drug	Maximum Daily Dose (mg/day)	Acceptable Intake NDMA (ng/day)*	Acceptable Intake NDMA (ppm)**	Acceptable Intake NDEA (ng/day)*	Acceptable Intake NDEA (ppm)**	Acceptable Intake NMBA (ng/day)*	Acceptable Intake NMBA (ppm)**
Valsartan	320	96	0.3	26.5	0.083	96	0.3

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

The FDA issued a General Advice letter to inform "applicants with an approved or pending application for an angiotensin II receptor blockers (ARB) drug product (DP), as well as holders of related drug master files (DMFs), of FDA concerns related to the presence of one or more toxic impurities in some ARB drugs." https://www.fda.gov/media/122643/download. In this letter, the FDA stated the following:

> Nitrosamine compounds are potent genotoxic carcinogens in several nonclinical species and are classified as probable human carcinogens by the International Agency for Research on Cancer (IARC). In fact, "N-nitroso" compounds are identified as a "cohort of concern" in internationally

> harmonized guidance, ICH M7, *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk*. ICH M7 recommends that known mutagenic carcinogens, such as nitrosamines, be controlled at or below the acceptable cancer risk level. Due to their known potent carcinogenic effects, and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their presence, FDA has determined that there is no acceptable specification for nitrosamines in ARB API and DP. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products.

All drug substance manufacturers should verify that their synthetic process can routinely make drug substance without the formation of nitrosamines in accordance with cGMP regulations at 21 CFR 211 subpart E. See also FDA guidance for industry, *ICH Q10, Pharmaceutical Quality System*. https://www.fda.gov/media/71553/download

My opinion that NDMA and NDEA should not be present in valsartan API is consistent with the FDA General Advice letter cited above and with the following statement made by the FDA in a General Advice letter to Prinston: "Due to their known potent carcinogenic effects, and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their presence, FDA has determined that there is no acceptable specification for nitrosamines in ARB API and DP. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products." ZHP00116661. This advice letter was forwarded to ZHP by Prinston. ZHP01591089.

The FDA made similar statements to Torrent in February 2019: "Due to their known potent carcinogenic effects, and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their presence, FDA has determined that there is no acceptable specification for nitrosamines in ARB API and DP. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products. TORRENT-MDL2875-00215093. A similar statement also appears in a letter to Watson Laboratories. TEVA-MDL2875-00154437.

Thereafter, the FDA provided further guidance to the manufacturers stating that "FDA expects that, when feasible, manufacturers of APIs and drug products should take reasonable steps to prevent or eliminate N-nitrosamines. When the elimination of N-nitrosamines is impractical, manufacturers should take appropriate measures to prevent unacceptable levels of N-nitrosamine impurities." ZHP00243853; TEVA-MDL2875-00733964; TORRENT-MDL2875-00204849. The elimination of N-nitrosamine impurities from valsartan drug substance is both feasible and practical as explained below.

TESTING METHODS FOR NDMA AND NDEA IN VALSARTAN

In response to the detection of nitrosamines found in valsartan containing medications, the FDA published testing methods with several options for industry, as well as regulators, to test for nitrosamines, including NDMA and NDEA. These FDA methods included the following: (a) Combined headspace method: a GC-MS method that allows determination of both N-

Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) simultaneously; (b) Combined direct injection method: a GC-MS/MS method that allows for determination of both NDMA and NDEA simultaneously; (c) Direct injection GC-MS method: a method that can detect NDMA, NDEA, N-Nitrosodiisopropylamine (NDIPA), N-Nitrosoethylisopropylamine (NEIPA), and N-nitrosodibutylamine (NDBA); (d) Headspace GC-MS method: a method that can detect NDMA, NDEA, NDIPA, and NEIPA; and (e) LC-HRMS method: a method that can detect NDMA, NDEA, NEIPA, NDIPA, NDBA, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA). The particulars for NDMA and NDEA testing methods may be found at https://www.fda.gov/media/117843/download.

These FDA published testing methods were not using new technology invented for the purpose of detecting nitrosamines in valsartan containing products. All these testing methods have existed for decades, long before the ZHP manufacturing processes using sodium nitrite were developed or used for the commercial production.

GENERAL RESPONSIBILITIES OF A DRUG COMPANY

Drug manufacturers, both manufacturers of the API/drug substance and manufacturers of finished dose drug product, have an absolute duty and responsibility to provide safe and effective drug products that meet strict quality standards. It is a generic drug manufacturers' responsibility to manufacture valsartan to be the same, chemically equivalent and pass the same quality and purity standards as the approved formulations and impurity profiles for Diovan or Exforge.

There are two basic application types for drug products: a "new drug application" commonly referred to as a "NDA" and an "abbreviated new drug application" commonly referred to as an "ANDA". A NDA is used for brand name drug products while an ANDA is used for generic drugs. A generic drug manufacturer must demonstrate that the API is the same as the name-brand (here, Diovan and Exforge). It was the generic drug manufacturers' responsibility to manufacture valsartan to be equivalent chemically and bioequivalent in the body and pass the same quality standards as Diovan. Generic drug manufacturers have an ongoing federal duty of sameness in their products which are supposed to be pharmaceutical and therapeutic equivalents to the name brand. 21 U.S.C. § 355(j). The FDA has explained that therapeutic equivalence equates to pharmaceutical equivalence if the drug has the same effect and safety profile https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.Specifically, the FDA provides under 1.2 Therapeutic Equivalence-Related Terms the following: (1) Pharmaceutical equivalents must **meet the identical compendial or other applicable standard of identity, strength, quality, and purity**, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. They may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, within certain limits, labeling; and (2) Approved drug products are considered to be therapeutic equivalents if they are pharmaceutical equivalents and among other requirements **they are manufactured in compliance with Current Good Manufacturing Practice regulations**. See https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface. Emphasis added.

The generic manufacturer must comply with cGMP regulations and demonstrate that their active ingredient(s) are the same as the Reference Listed Drug ("RLD") and have identical strength, quality, purity, potency (and where applicable, other characteristics) as the RLD. See § 355(j)(2)(A)(ii) and *e.g.*, 21 C.F.R. 314.3(b). API manufacturers file Drug Master Files (DMFs) with the FDA. DMFs contain confidential, detailed information about the manufacturing of the API such as the proprietary synthesis process for making the drug substance. Finished dose manufacturers reference the DMF in ANDAs by Letters of Authorization (LOA) from the drug substance manufacturer. See 21 CFR 314.42 (c) The drug substance manufacturer has the right to amend the DMF to provide updated information whenever necessary. Drug substance manufacturers should notify finished dose manufacturers with LOA's of any changes to the DMF that could affect the drug product.

cGMP STANDARDS

The regulatory standard for ensuring pharmaceutical quality is the Current Good Manufacturing Practice (cGMP) regulation for human pharmaceuticals per the FDA. These cGMP regulations set forth minimum requirements for drugs concerning the methods, facilities, and controls to be used in manufacturing, processing, and packing of a drug product. cGMP regulations are intended to make sure that a product is safe for use, and that it has the ingredients and strength it claims to have. https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations. cGMP regulations set forth systems to assure proper design, monitoring, and control of manufacturing processes and facilities. It is required that drug manufacturers follow the cGMPs to assure the purity, identity, strength, and quality of their manufactured drug products by requiring they properly control manufacturing operations. A drug is deemed adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." See 21 U.S. Code § 351.To comply with cGMP regulations, drug manufacturers have a duty to establish strong quality management systems, obtain appropriate quality raw materials, establish robust operating procedures, detect, and investigate product quality deviations, and maintain reliable testing laboratories. The requirement for a formal system of controls at a pharmaceutical company, if adequately put into practice and followed, is intended to prevent instances of impurities and contamination such as with valsartan.

ADULTERATED DRUGS

A drug is adulterated if the methods used for its manufacture and processing do not conform to or are not operated or administered in conformity with current good manufacturing practice (cGMP) to assure that such drug meets the requirements as to safety and meets the quality and purity characteristics, which it purports or is represented to possess. A drug is also deemed adulterated if it purports to be or is represented as a drug which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below the standard set forth in such compendium. See Section 21 USC 351 (a) and (b). The USP valsartan monograph is an official

compendium that generic valsartan must meet with regard to its quality and purity. NDMA and NDEA are not accepted impurities of valsartan. Valsartan with NDMA and/or NDEA impurities differs from the quality and purity standards set forth in the USP valsartan monograph. Valsartan with NDMA and/or NDEA would constitute an adulterated drug.

Notably, complying with the USP monograph impurity profile is not in itself an adequate control for impurities. Prinston recognized this fact stating: There is a USP method for testing other related compounds in the drug substance monograph. However, the USP method was not acceptable because it could not completely resolve other potential impurities. For this reason, DMF holder (Zhejiang Huahai) developed an in-house HPLC method which is compared with the USP method in Table 6 below. ZHP01451842, 01451855.

However, ZHP as well as the finished dose manufacturers using ZHP API failed to recognize that the testing of valsartan drug substance must include testing for nitrosamines using GC-MS or LC-MS to detect impurities like NDMA and NDEA given the risk of nitrosamine formation from chemical reactions during the manufacturing process.

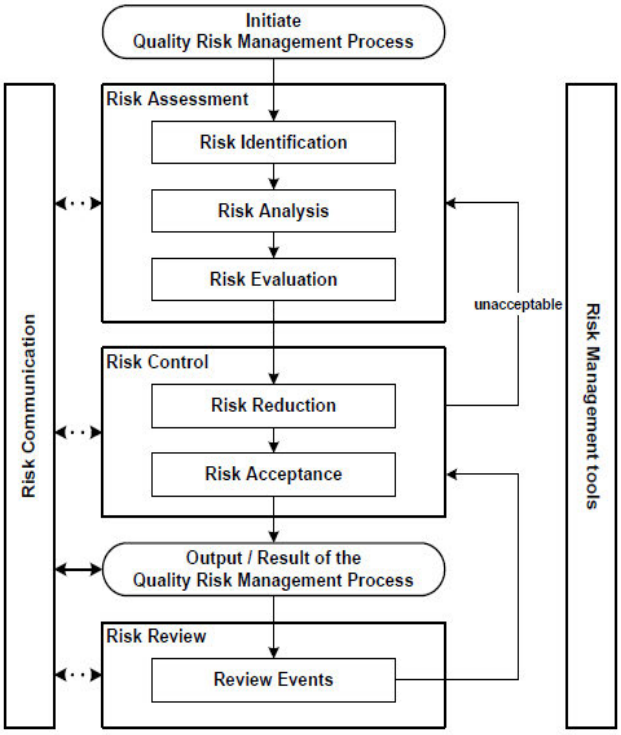
NEED FOR RISK ASSESSMENT

When deciding on the method to manufacture an active pharmaceutical ingredient (API) and/or the finished drug product, a formal risk assessment must be performed to determine that the appropriate raw materials, solvents, excipients, and manufacturing processes are used to manufacture the drug. Only proper risk management by drug substance and drug product manufacturers during development and manufacture will identify issues and control quality to ensure safe drug products for use by patients. A thorough, comprehensive risk assessment plan must be developed and followed to ensure detection of any unintended impurities in the drug product. This is an ongoing duty for the lifecycle of the drug substance and product during the entire period of manufacturing and sale. ZHP representative, Dr. Li, testified that risk assessment is part of the ongoing process of the manufacture of the drug substance. Dr. Min Li's Dep. Tr. at 233, 4/20/2021.

The FDA identifies an appropriate risk management system in its Q9 Quality Risk Management, Guidance for Industry. See Guidance for Industry, Q9 Quality Risk Management, Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) June 2006. https://www.fda.gov/media/71543/download

The FDA provides the following flowchart in its Guidance showing the steps of a "typical quality risk management process":

Figure 1: Overview of a typical quality risk management process



The identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards is part of an Effective Risk Assessment. The FDA identifies three fundamental questions to be considered: 1. What might go wrong? 2. What is the likelihood (probability) it will go wrong? 3. What are the consequences (severity)? These questions, when considered and correctly answered, will appropriately identify, reduce and/or eliminate risks. https://www.fda.gov/media/71543/download, page 4

A drug manufacturer must develop, implement and follow a quality risk management system. Proper risk management provides the tools and practices to identify and control potential quality issues when developing and manufacturing drug products. Quality and safety of the finished drug product can only be ensured when effective risk management is enforced. An important part of an effective risk management program is identifying and incorporating proper testing throughout the manufacturing process. https://www.fda.gov/media/71543/download, page 4

Risk management procedures are utilized in the decision-making process when a potential or actual quality problem is identified requiring a thorough and effective investigation into the problematic issue and to determine its cause. Risk assessment is an ongoing requirement during a manufacturer's making of drug substances and drug products including during their annual product reviews. Product reviews are required to be conduct at least annually "to determine the need for

changes in drug product specifications or manufacturing or control procedures." See 21 CFR 211.180(e).

Each drug substance manufacturer, including the Defendants in this case, is required to conduct an effective risk assessment to determine what, if any, unintended chemicals could be formed because of the drug synthesis (manufacturing) process. The drug manufacturers must predict based on the chemical synthesis process what impurities could form. In some instances, a force degradation study is helpful to evaluate impurity creation.

It is well-accepted in the field of organic chemistry and chemical literature that when mixing two compounds an impurity may result. In that case, the process chemist needs to alert the quality control department to develop a method to test for the potential impurity and monitor its potential formation during the drug substance manufacturing process. The final drug substance should also be tested for the potential impurity. This is especially important for mutagenic and carcinogenic compounds.

When a change is proposed for a validated manufacturing process, a risk assessment must be performed to evaluate the potential impact of a proposed change on the quality of the final product for intermediates, API or finished dose. Sound scientific judgment and analysis must be used to ascertain any additional testing and validation studies that are required to justify the proposed changes to a validated manufacturing process. The FDA's three basic questions to be asked and answered are again: What might go wrong? What is the likelihood (probability) it will go wrong? and What are the consequences (severity)? The drug manufacturer through its risk assessment must determine (based on the proposed changes) what additional testing is needed to answer these questions and then conduct the testing to ensure that the changes will not negatively impact the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency of the drug being developed or manufactured.

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ZHP filed DMF 020939 in September 2007 setting forth their chemical synthesis process called the **Tin process**. PRINSTON00078386. The **Tin process** used [redacted] and sodium azide instead of tributyl azide. PRINSTON00078386. For this process, [redacted] was used as the solvent in Step 4 (also known as the crude step) catalyzed by [redacted] No dimethylamine or its derivative reagents were used. Triethylamine hydrochloride was not used in this process, and no sodium nitrite was used to quench after the reaction. PRINSTON00423595. On April 19, 2011, ZHP filed its first amendment for the Tin process, with the only change being an update on stability data, no manufacturing changes were made. PRINSTON00077824.

An evaluation of the Tin process, which is similar to the Diovan synthetic process, reveals that it is not expected to form NDMA or NDEA since triethylamine, dimethylamine or other materials that might introduce secondary amines are not used and are not potential degradation products of the substances used, and sodium nitrite is not used to quench. PRINSTON00075818.

Here is the schematic of the synthetic route for the ZHP manufacture of valsartan using tin chloride (ZHP01661566; 1661569 to 1661574 dated 9/20/2007):

REDACTED

REDACTED

REDACTED

In the tin process, ZHP does not use DMF solvent (Dimethylformamide) and $NaNO_2$. DMF solvent gives rise to Dimethylamine. $NaNO_2$ is the precursor to nitrous acid (HNO_2) which is the key precursor to the nitrosating agents namely positively charged NO^+ (Nitrosonium ion). Positively charge NO^+ reacts with any secondary, tertiary amines to form NDMA or NDEA. In the Tin process no NDMA or NDEA is expected. In its investigation report, ZHP acknowledged that "no NDMA or NDEA will be formed in Tin process." PRINSTON00075870.

Scheme 1 (ZHP02336472) below shows another example of a route of synthesis with the final synthetic step (exclusive of work-up and purification) involving the reaction of a cyano group on the biphenyl ring with an azide, for example, tributyl tin azide:

REDACTED

Importantly, the above routes of valsartan synthesis do not involve the use of DMF solvent or sodium nitrite so the formation of nitrosamines, such as NDMA or NDEA, is not expected. Another example of an alternative synthesis of valsartan was published by Wang. See *Wang et al., An Improved Synthesis of Valsartan, Organic Process Research and Development, ACS Publications., American Chemical Society, 2011, 15, 986-988.*

TRIETHYLAMINE HYDROCHLORIDE (TEA) PROCESS

ZHP decided to move away from using the Tin process and submitted a DMF (DMF 23491) for the TEA process in January 2010. PRINSTON00073120. The TEA process changed Step 4 (Crude Step) by using triethylamine hydrochloride/sodium azide instead of [redacted] sodium azide and toluene as a solvent instead of [redacted] PRINSTON00075819. This change in process from [redacted] /sodium azide to triethylamine hydrochloride/sodium azide was made to lower manufacturing costs and toxicity risk. PRINSTON00073120. In response to a DMF deficiency from the FDA, ZHP filed an amendment to DMF 23491 on February 4, 2011. PRINSTON00072213; 72215. In this amendment, ZHP represented to the FDA that "potential impurities can be routinely controlled" and provided a "summary of in-process test results used to control the various reactions leading to the final drug substance". PRINSTON00072213; 72215. ZHP filed another amendment to DMF 23491 adding a "quenching procedure after tetrazole reaction with sodium nitrite solution/hydrochloric acid to guarantee azide is destroyed thoroughly and to minimize the risk of residual azide carry-over into the final drug substance" on April 16, 2012. PRINSTON00071518. ZHP filed a third amendment to DMF 23491 on March 1, 2013, which included no changes to the process. PRINSTON00072213; 72216.

ZHP represented in its DMF filing that the TEA process produced valsartan drug substance free of genotoxic impurities. PRINSTON00080011

The synthetic route of the Triethylamine Hydrochloride Process without quenching (SOLCO00026845-SOLCO00026848) is depicted below:

ROUTE OF SYNTHESIS

REDACTED

REDACTED

REDACTED

Notably, the above TEA hydrochloride route of valsartan synthesis without quenching does not involve the use of DMF solvent or sodium nitrite so the formation of nitrosamines, such as NDMA or NDEA, is not expected.

ZHP's synthetic route of the Triethylamine hydrochloride process with quenching with sodium nitrite is depicted in Figure 1a-2 (PRINSTON00074772) copied below.

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During the crude synthesis step # 4, sodium azide (NaN_3) is used to convert a nitrile moiety R-CN to a tetrazole shown as a 5 membered ring with 4 Nitrogen atoms. Because sodium azide is a potential explosive, all unreacted (excess) sodium azide must be neutralized, with a suitable neutralizing agent such as sodium nitrite ($NaNO_2$). Under mild acidic condition, sodium nitrite converts to HNO_2 which becomes a source for positively charged NO^+ (a powerful nitrosating agent). This quenching reaction carried out in the presence of the valsartan intermediate can result in the generation of NDEA during the tetrazole formation and the quenching of the excess sodium azide. LP1375 – PRINSTON00158177, 00158191.

During this manufacturing process the triethylamine hydrochloride that is used in synthetic step #4 gets nitrosated and undergoes elimination of HNO followed by hydration and elimination of water and acetaldehyde to give rise to diethylamine which then easily gets nitrosated again to form NDEA as illustrated below.

REDACTED

ZINC CHLORIDE PROCESS

ZHP continued in its quest to change its valsartan synthesis process to improve reaction yield and reduce costs. On November 27, 2011, ZHP initiated an internal critical change request. This initial characterization of this change as "**critical**" appears in ZHP's internal documents. ZHP00063901, 63902; ZHP02267364, 67365. This critical change was "making changes to the Valsartan manufacturing process to reduce current conversion rate (60%-70%) of the known isomer impurity D-Valsartan in the final API and increase batch yields." PRINSTON00073432.

ZHP filed an amendment to DMF 23491 on December 10, 2013, which described a process which became known as the "**Zinc Chloride**" process. PRINSTON00073120. In this amendment, ZHP changed the chemical reagent used in Step 4 from triethylamine hydrochloride to zinc chloride. PRINSTON00073120. ZHP also further deployed DMF solvent and MTBE solvent (Methyl t-butylether) to Steps 3 and 4 to "facilitate the process" and stated that they would be "successively removed" later in the process. PRINSTON00073120.

The Zinc Chloride process significantly changed the chemicals used in the synthetic process, along with the risk profile of the synthetic scheme. This had a substantial potential to adversely affect the identity, quality, and purity of the drug product, and adversely affect the safety or effectiveness of the drug product. The amendment changed the chemical reagent used in Step 4 and added DMF and MTBE solvent to the chemical synthesis process.

ZHP represented in its DMF filing that the Zinc Chloride process produced valsartan drug substance free of genotoxic impurities. HUAHAI-US00007752.

The synthetic route of the Zinc Chloride Process is depicted in Figure 1a-3 (PRINSTON00074773) which is copied below.

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As can be seen above in the crude step (step #4), ZHP chose to use DMF solvent which has a potential to degrade and form dimethylamine. ZHP01344159. Once again, all the ingredients for the formation of NDMA are present in step 4. DMF solvent often contains dimethylamine. Presence of sodium nitrite and dimethylamine from solvents like DMF can contribute to NDMA formation. HNO_2 is plentiful in this reaction and the manufacturer did not heed the obvious risk of nitrosamine formation.

USE OF SODIUM NITRITE, NITROUS ACID, ACIDIC CONDITIONS, AND SUBSEQUENT NITROSAMINE FORMATION

Using DMF solvent in the process should have raised concern for the possible formation of nitrosamines because DMF solvent has been long known to decompose into dimethylamine. See *Purification of Laboratory Chemicals, Armarego, WLF (4th Edition 1996; 6th Edition 2009).* In addition, HNO_2 is a well-established nitrosating agent which must be carefully monitored if used. The presence of dimethyl or triethylamine should have been avoided to prevent formation of nitrosamines. The QC department should have been alerted by the chief process chemist to monitor for nitrosamine impurities as part of the manufacturing process.

During the development of Process II ($ZnCl_2$) which used a high excess of NaN_3 and a high excess of $NaNO_2$ as a quenching agent, a major red flag should have been raised as this combination of processes is known to cause potential side reactions forming nitrosamines. Both the synthetic and process chemistry divisions overseeing this change should have recognized this risk and tested as part of good manufacturing practice to make sure nitrosamines were not being formed.

NDMA AND NDEA IN ZHP VALSARTAN DRUG SUBSTANCE

In its Investigation Report, ZHP reported the results of its NDMA and NDEA testing for its valsartan drug substance referencing the manufacturing process used. ZHP02217257. The drug substance made with the TEA hydrochloride process without $NaNO_2$ quenching had no detectable NDMA or NDEA. However, no valsartan finished dose using the API made by this process was sold in the United States.

Three validation batches of drug substance made with the TEA hydrochloride process with $NaNO_2$ quenching were tested by ZHP and were found to have significant levels of NDEA ranging from 13.51 to 18.83 ppm.

Three validation batches of drug substance made with the $ZnCl_2$ process were tested by ZHP and were found to have significant levels of NDMA ranging from 51.6 to 76 ppm, with one batch also tested for NDEA with a result of 4.2 ppm.

Batches manufactured by the TEA hydrochloride process with $NaNO_2$ quenching after switching from the $ZnCl_2$ process were found to have NDEA levels ranging from 3.89 to 24.64 ppm and also NDMA levels ranged from 0.16 to 4.40 ppm.

Batches manufactured by the $ZnCl_2$ process were found to have NDMA levels ranging from 67.67 to 89.10 ppm and NDEA with levels ranging from 0.10 to 0.44 ppm.

All batches referenced in the Investigation Report which were manufactured with the TEA hydrochloride with $NaNO_2$ quenching process and $ZnCl_2$ process had either NDMA, NDEA or both. In general, batches made with the $ZnCl_2$ process had higher NDMA levels while batches made with the TEA hydrochloride with $NaNO_2$process had higher NDEA levels. This would be expected given the route of synthesis for each process. The report also discusses the levels found as they relate to the switching of the production between the different processes, and the carry-over of either NDMA or NDEA contamination from one process to the other. ZHP02217258 This cross-contamination was acknowledged by Dr. Min Li during his deposition wherein he testified that some of the NDMA in ZHP's valsartan API made from the TEA process was due to cross-contamination from ZHP's valsartan API made from the zinc chloride process, as they shared the same manufacturing line (Dr. Min Li's Dep. Tr., pgs 77-80, 4/20/2021). Genotoxic contamination caused by inadequate cleaning of the equipment between different manufacturing processes, and failure to test for potential residual nitrosamines, would not be consistent with good manufacturing practices, and is a violation of cGMP.

LACK OF PROPER RISK ASSESSMENT

It is my opinion that ZHP failed to follow good manufacturing practice when it failed to conduct a proper risk assessment upon making changes to the manufacturing process (also known as the "Route of Synthesis" or ROS) and continued to fail to conduct ongoing risk assessments when using the TEA hydrochloride and $ZnCl_2$ processes to manufacture valsartan drug substance for commercial sale. ZHP incorrectly determined that any risks associated with changes in the chemical ingredients such as types of degradants and by-products were empirically negligible. Knowledge of basic organic chemistry suggests that changes to the chemical reagents of a reaction would alter the degradant/by-product profiles requiring such risks to be critically evaluated. ZHP failed to conduct a thorough risk-based evaluation of the possible formation of nitrosamines resulting from their proposed process changes. ZHP demonstrated a lack of proper scientific judgment in process operations leading to the manufacture of an unsafe valsartan API. It is the duty of organic process chemists working in the pharmaceutical industry to be versed in the study of chemical reactions and pertinent scientific literature to be able to properly evaluate ROS for the potential formation of unintended impurities like NDMA and NDEA. It is the ongoing responsibility of drug substance/drug product manufacturers to conduct ongoing risk assessments of the manufacturing process and use adequate methods to test and detect impurities including genotoxic impurities such as NDMA and NDEA.

Changing the route of synthesis (ROS) process from [redacted] to sodium azide (NaN_3) should have triggered a risk assessment along with developing a process that used a large excess of sodium azide (NaN_3), which in turn would have to be quenched with a large excess of sodium nitrite ($NaNO_2$) under acidic condition to reduce the chance of potential explosion by sodium azide (NaN_3). There is a substantial risk during this step, HNO_2 is formed which can nitrosate trimethylamine, dimethylamine, and form NDMA, as well as nitrosate triethylamine or diethylamine to form NDEA. This is a well-established textbook reaction that should be recognized by process chemists working in the pharmaceutical industry for companies like ZHP

who manufactured API (drug substance) and finished dose drug manufacturers. See https://chem.libretexts.org/Ancillary_Materials/Demos_Techniques_and_Experiments/Chemical_Safety/Reagent_Specific_Hazards/Sodium_Azide

In both the TEA hydrochloride process and $ZnCl_2$ process for valsartan there were significant changes in valsartan's synthesis. It was vital for the organization to consider potential impurities generated due to this process change by GC-FID and by a more sensitive technique, such as GC-MS. ZHP provided no explanation for why GC-MS, a workhorse technique used by organic chemists for decades and which is available in many undergraduate chemistry labs and common in pharmaceutical laboratories, was not used to analyze impurities in valsartan after a process change. In my opinion, the only reason one would choose to use a GC-FID instead of GC-MS would be a lack of understanding of chemical processes and reactions, and/or to reduce chances of detection of finding impurities. That is exactly what happened here.

The association of NDMA and other nitrosamines with nitrites/nitrates is long known and should have been foreseen during the process change at ZHP that entailed using a large amount of nitrite for quenching. ZHP's risk assessment should have led them to monitor formation of multiple potential nitrosamines including NDMA and NDEA.

ZHP's Standard Management Operating Procedure had a written risk management process in place which involved risk identification, risk analysis, risk evaluation, and risk reduction. ZHP00000418-ZHP00000470; ZHP00703030; ZHP01793452. ZHP's risk management team was required to be qualified with the following skills: hazard analysis, potential hazard analysis, identification of the hazards that should be controlled, the ability to propose control measures, develop monitoring and verifying procedures, to propose CAPA for deviations, and review Quality Review Management protocol. ZHP00000418-ZHP00000470;ZHP01793454. However, this obvious nitrosamine hazard was not identified, controlled, or monitored as part of all phases in the life of the product including the manufacturing process. Scientific research of each of the reagents would have alerted them to several potential hazards. For example: sodium azide is explosive and mutagenic. A simple review of the properties of $NaNO_2$ available in scientific literature and textbooks would have shown the potential for formation of nitrosamine. ZHP's risk management team failed to follow their own standard operating procedures and failed to recognize and test in response to a clear quality risk.

It is my opinion expressed with a reasonable degree of scientific certainty, that if ZHP complied with cGMP and conducted a proper risk assessment of its manufacturing processes and conducted proper risk assessments during their ongoing manufacture of the drug substance, they would have discovered that NDMA and NDEA could be formed as a result of the changes in the chemical synthesis process and in fact were forming. During the course of its manufacture of valsartan drug substance, ZHP should have required testing for NDMA and NDEA. ZHP could also have made changes to their chemical synthesis process to eliminate NDMA and NDEA impurities. This discovery would have resulted in the use of testing methods such as a direct injection GC-MS method, headspace GC-MS method, combined headspace method, combined direct injection method, and/or LC-HRMS method which would detect NDMA and NDEA. These testing methods should have been used on every valsartan API batch to ensure that it did not contain NDMA or

NDEA to maintain the safety and integrity of the drug product. Similarly, if the finished dose manufacturers had conducted a proper risk assessment of the synthetic route used by ZHP to manufacture the API, they too would have discovered that NDMA and NDEA can be formed.

The valsartan drug products which contained NDMA and NDEA as manufactured by the defendants were not the same as the formulation of its brand name counterpart, Diovan, which had a synthetic process using [redacted] like the original ZHP process which did not have the potential based on the route of synthesis (ROS) to form NDMA or NDEA. The Defendants through their ANDA were given permission by the FDA to manufacture valsartan equivalent to the approved name-brand referenced listed drug, not valsartan containing levels of NDMA and NDEA. The referenced listed drug for valsartan is Diovan which does not contain NDMA or NDEA. Defendants' valsartan containing products were not the generic, pharmaceutical, therapeutic and chemically equivalent of Diovan or Exforge because they contained NDMA and NDEA.

ZHP's utter failure to conduct an adequate risk assessment at any point during their production and manufacture of valsartan was noticed by the FDA in its 483 Report stating that ZHP's change control system was inadequate because ZHP failed to evaluate all changes that may affect the production and control of intermediates or API; ZHP failed to conduct and document a formal risk assessment for Change "Request PCRC-11025 to evaluate the potential impact of proposed changes on the quality of the intermediates or the final API; ZHP was in error for initiating validation on a commercial scale without conducting a formal risk assessment to evaluate the potential impact of changes to their validated manufacturing process on the quality of intermediates and APIs; ZHP did not have an adequate change control system requiring scientific judgment to determine the additional testing and validation studies that were appropriate to justify changes to a validated manufacturing process; and ZHP did not always have data to support approval of changes to validated processes. PRINSTON00073432.

ZHP's lack of proper risk assessment also resulted in several other FDA Quality System Inspectional Observations noted in its 483 including:

> Observation One included the fact that ZHP had utilized an outside laboratory to conduct research but failed to enter into a quality agreement with them to ensure validation and qualification of methods and instruments.
>
> In Observation Two, the FDA stated that "validation of production processes, cleaning procedures, analytical methods, and in-process control test procedures were not always adequate."
>
> In Observation Three, the FDA reported that "the system for managing quality to ensure confidence that the API will meet its intended specifications for quality and purity is not adequate in that your quality unit lacks written procedures and the authority and responsibility to ensure all critical deviations are thoroughly investigated."
>
> Observation Four stated that "the quality unit does not always fulfill the responsibilities of the quality unit to release or reject all APIs."

Observation Five stated that their cleaning procedures were inadequate,

Observation Six stated that equipment was not being maintained.

Observation Seven stated that procedures and preventative maintenance on equipment were not adequate or did not exist.

Observation Eight stated that substances used during operation of their equipment were not always food grade.

Observation Nine stated that "sampling plans, and test procedures are not always scientifically sound and appropriate to ensure raw materials, intermediates and APIs conform to established standards of quality."

Observation Ten stated that ongoing testing and monitoring was not accurate.

Observation Eleven stated that deviations were not always reported, evaluated, or investigated. PRINSTON00073432-73442.

The FDA issued a warning letter on November 29, 2018 following the 2018 EIR and 483 report summarizing ZHP's significant deviations from cGMP for API. ZHP00008243. The warning letter addressed the inadequacy of ZHP's response to the 483 report and noted two main observations requiring response. ZHP00008243. The first was "failure of your quality unit to ensure that quality-related complaints are investigated and resolved." ZHP00008243. The FDA identified two specific instances of customer complaints regarding unknown peaks that were identified as NDMA, which ZHP failed to properly investigate. ZHP00008243. The second was "failure to evaluate the potential effect that changes in the manufacturing process may have on the quality of your API". ZHP00008243; 8246. One of the events the FDA identified was the November 2011 Critical Change Request that ZHP made without conducting a proper risk assessment on impurities. ZHP00008243; 8246. The FDA concluded the warning letter by notifying ZHP that their firm had been placed on import alert as of September 28, 2018, and that until corrective actions were taken and there is compliance with cGMP, the FDA may withhold all approval of any future drug application. ZHP00008243; 8248. This is the FDA language in the letter:

> FDA placed your firm on Import Alert 66-40 on September 28, 2018.
>
> Until you correct all deviations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

ZHP claimed they lacked understanding of the chemistry involved and failed to conduct an appropriate risk assessment. In an email exchange, ZHP stated its failure to conduct a proper risk assessment was due to an excusable lack of understanding of the chemistry involved. ZHP00406066- ZHP00406069. This explanation was not accepted by the FDA.

In an email dated July 27, 2017, ZHP employee Jinsheng Lin referenced an investigation of an impurity in crude irbesartan, another ARB drug. In this email, Dr. Lin acknowledged the impurity

he was investigating was very likely an "N-NO compound" which "is similar to the N-nitrosodimethylamine that occurs in valsartan when quenched with sodium nitrite." Min Li Ex. ZHP-296 (4/20/2021); ZHP00190573-00190574. Even having this knowledge, ZHP did not test each batch of valsartan API it manufactured for NDMA which is a violation of FDA's cGMP (current good pharmaceutical manufacturing practices) and sound chemistry practice.

The July 27, 2017 email also referenced a Zhejiang Second Pharma Co. Ltd. patent for a method for preparing valsartan with an application date of November 8, 2013, wherein it was explained that valsartan can be deacylated and then nitrosated forming a molecule named valsartan impurity K ,a "highly toxic nitroso compound". This provided notice to ZHP that nitrosation could occur during the synthesis of Valsartan, and they should investigate the formation of other nitrosated amines such as NDMA and NDEA. Knowledge of valsartan impurity "K" should have initiated a risk assessment and testing of their own valsartan synthetic processes to determine if other nitrosamines may be occurring in the final drug substance. If ZHP conducted this risk assessment and tested the valsartan drug substance nitrosamines, they would have discovered the NDMA and NDEA. ZHP01812101-ZHP01812109.

After discovery of NDMA and NDEA in the drug substance, the ZHP Quality Management Department acknowledged their lack of risk assessment stating that NDMA formation "based on the chemistry involved" "was not foreseen due to lack of experience" and further, that they failed "to conduct a thorough risk-based evaluation on possible impurity profiles" which together resulted in failure to identify the potential to generate NDMA in Valsartan API process change (PCRC-11025)." ZHP00406066-406069. QA further wrote that when Novartis initially alerted them to the presence of NDMA, they still failed to identify and consider several factors that could contribute to the presence of NDMA. ZHP00406066-406069.

FAILURE TO DISCOVER THE NDMA AND NDEA DURING RESIDUAL SOLVENT ANALYSIS

Residual organic solvent testing was performed on the valsartan API via gas chromatography (GC method) as part of the manufacturing process. ZHP01460255-1460258. The ZHP GC method used a flame ionization detector (FID) and head-space injection.

Gas chromatography is an analytical chemistry technique used to separate, detect, and quantify small volatile compounds that can be vaporized without decomposing. GC works by using an inert gas, such as helium, nitrogen or hydrogen to carry a vaporized sample through the GC system. The sample is injected into the GC, and it travels through an analytical column which is heated in an oven during the analysis. The outlet of the column is inserted into the detector which responds to the chemical components eluting from the column to produce a signal. The volatile compounds elute at different times due to their different chemical properties such as ease of vaporization, boiling points, polarity, molecular weight, and column temperature. The signal is recorded by the acquisition software on a computer to produce a chromatogram. The resulting chromatogram is a two-dimensional plot with the vertical axis giving concentration in terms of the detector response, and the horizontal axis representing the retention time. The detector gives a response as a peak whose height should be ideally dependent on the concentration of the particular component.

GC is used during the drug manufacturing process to detect and measure the volatile compounds that should not be present or only present in very limited quantities in the final drug substance. For valsartan, the ZHP chromatograms were designed to detect and measure for residual solvents such as methanol, ethanol, ethyl acetate, benzene and toluene.

Since NDMA and NDEA are semi-volatile compounds, both are readily capable of being detected by GC-FID, however, GC-MS would have provided much higher sensitivity. The GC chromatograms created by ZHP during their residual solvent testing revealed many unknown peaks. These chromatogram peaks are of a size that required further investigation to determine what was causing them. Many of those impurities were left unidentified as noted by the FDA and Prinston in Response to the FDA DMF Information Request Letter. PRINSTON00162349-162406, 00162365; ZHP00079913-ZHP0079945, ZHP0079936. The failure by ZHP to utilize GC-MS to be able to reduce the number of impurities they would observe in a straight-forward residual solvent analysis, and deprived ZHP of the appropriate testing to look for and identify the NDMA and NDEA.

During its manufacture of valsartan drug substance, ZHP did not properly investigate the unknown peaks and made no determination as to what chemical compound or phenomenon was causing these peaks. ZHP clearly failed to follow current good manufacturing practice and ICH's guidance, when it simply assumed that these unknown peaks were the result of column or injector port bleeding, sample diluent decomposition, thermal decomposition or pyrolysis of analytes in the GC injector port. ZHP01859921-ZHP01859933. Finding peaks of this size and location mandated assessment of the manufacturing process to identify potential impurities including NDMA and NDEA, and investigation by GC-MS to affirmatively identify their cause.

If such peaks would have been properly investigated, ZHP would have learned that NDMA and NDEA were present in their valsartan drug substance. This was underscored when ZHP's potential customer, Novartis, discovered the unknown peaks upon conducting a routine GC-FID residual solvent testing, which it followed with GC-MS to affirmatively identify NDMA. ZHP00400281. ZHP00400288. ZHP00388706. NDEA could also be easily identified via GC-MS. ZHP02733180. So if Novartis observed NDMA using GC-FID, how did ZHP who should have performed residual solvent testing on every drug substance batch miss it? ZHP did not identify NDMA and NDEA because they failed to follow cGMP, failed to conduct a proper risk analysis, and failed to question and identify unknown peaks through testing.

ACTIONS THAT COULD HAVE BEEN TAKEN BY ZHP

ZHP should have recognized that nitrosamines such as NDMA and NDEA were present in its final drug substance using the TEA hydrochloride and $ZnCl_2$l processes, and as such, returned to using its original Tin process or the TEA hydrochloride process without quenching.

ZHP also could have performed the quenching of azide without the presence of the drug substance. This concept was discussed by Prinston Pharmaceuticals in the Request for Comments and Advice shown below using the $ZnCl_2$ process as an example. ZHP01495187.

1.12.4 Request for Comments and Advice

REDACTED

Figure 3: The relevant steps in Huahai's Valsartan ROS where NDMA can be formed during Step 4 as illustrated above

As explained by Prinston: "the step that will most likely generate NDMA is the crude step of Process II ($ZnCl_2$) where dimethylformamide and nitrous acid exist simultaneously to render the nitrosation reaction." As the quenching takes place in the presence of the product, NDMA formed during the quenching step can be present in the product and can carry over into the final product. Prinston explains that "the easiest way to avoid the formation of NDMA in the current drug substance process is to perform the quenching **without** the presence of the product by separating the organic phase (containing the product of the step) from the aqueous waste (containing unreacted azide) and then performing quenching only on the aqueous waste. Prinston acknowledges that this approach can be done without changing the manufacturing process. ZHP01495187-1495188. Performing quenching without the presence of the drug product could be applied to the TEA hydrochloride process as well.

ZHP also could have added a step to the manufacturing process requiring GC-MS or LC-MS testing of every batch of valsartan drug substance to ensure that it did not contain nitrosamines, including NDMA and NDEA.

ZHP DEVIATION INVESTIGATION REPORTS

After being alerted to the presence of NDMA in the valsartan drug substance by Novartis, ZHP began an internal investigation into the cause of the nitrosamine contamination. ZHP's investigation generated several reports. Importantly, the discoveries by ZHP should have been part of their original risk assessment for the proposed changes to the manufacturing process, and part of their ongoing risk assessment while manufacturing the valsartan API using the TEA hydrochloride and $ZnCl_2$ process. A proper risk assessment would have revealed that NDMA and NDEA were likely to form, and in fact, did form during the manufacture of valsartan API.

Deviation Investigation Report 18001. After learning from Novartis the unknown peak seen on GC was potentially NDMA, ZHP began a deviation investigation on June 6, 2018. ZHP00007221-7329. ZHP developed a GC-MS testing method for NDMA. Three batches of valsartan API were tested by ZHP on June 11th. NDMA was present in all three batches in substantial amounts, 62.9 ppm, 44.8 ppm, and 90.1 ppm.. ZHP00007221-7224. ZHP noted that the probable cause of the formation of NDMA was due to the chemical synthetic process, and was most likely generated during the "azide quenching by nitrous acid" step. ZHP00007221-7329, 7227. DMF solvent was noted to be susceptible to decomposition under high temperature to produce dimethylamine. ZHP00007227-7228. The quenching of azide by sodium nitrite / nitrous acid process can form NDMA as a result of the reaction between dimethylamine and nitrous acid. ZHP00007241.

ZHP recognized residual solvents were being tested by GC-FID method, which is not suitable for detecting NDMA "at such trace level". ZHP00007234. It is my opinion that using an analytical instrument with a lower detection limit such as GC-FID is inappropriate and is not consistent with cGMP best practices when unknown peaks are seen, particularly when a potent carcinogenic nitrosamine may be involved.

Deviation Investigation Report 18003. ZHP performed a deviation investigation on the TEA process. ZHP00276288-276424. In this report, ZHP reiterated its findings in DCE 18001 regarding the Zinc Chloride process noting that the DMF solvent used was susceptible to decomposition via thermal or hydrolysis which can produce dimethylamine. ZHP00276300. Also, during the quenching of azide with nitrous acid during the Zinc Chloride process, NDMA can form between dimethylamine and nitrous acid. ZHP00276300. A few pages later in the report, however, ZHP indicated that testing of 55 batches manufactured via the TEA hydrochloride process, all had detectable levels of NDMA. ZHP00276331. ZHP further investigated the TEA hydrochloride process and found that NDEA is likely formed in Step 4 crude stage. ZHP00276343. In Step 4, toluene and triethylamine are used for the tetrazole formation. ZHP00276343. HNO_2 can react with triethylamine to form NDEA. ZHP00276343. ZHP developed a GC-MS testing method for NDEA. ZHP00276334. When using this method, ZHP found NDEA levels ranging from 0.03 to 18.83 ppm in 6 batches of valsartan API made with the TEA hydrochloride process. ZHP00276335.

Deviation Investigation Report 18004. During an inspection on September 10, 2018, the EU authority completed a test on a valsartan drug substance batch number C5271-17-288 finding approximately 96.6 ppm of NDMA present. ZHP00406894-6901. This result was not consistent

with prior results reported by ZHP for this batch finding no NDMA. ZHP00406897-6901. This inconsistency was the subject of Deviation Investigation Report 18004. ZHP00406894-406932.

In this report, ZHP confirmed all persons involved in the previous testing were trained and qualified in instrument operation and test method, the instrument used was effectively calibrated and analysis was performed within the calibration period, the analytical testing method used by Haotian Testing was QRC-18029(R), and that no anomaly was found during the calculation process. ZHP00406905-406906. However when conducting GC-MS testing on this batch, ZHP found clear NDMA peaks which were not present and/or identified in their initial testing. ZHP00406900. Upon retesting, ZHP found NDMA levels of 72.8 ppm. ZHP00406901. ZHP speculated that the root cause of this deviation was that "the sample did not enter the detection system." ZHP00406906. ZHP stated it was "possible that the sample did not enter the detection system due to poor seal performance of the headspace vial." ZHP00406909. ZHP noted that the specific processes for sealing the headspace vial was not detailed in the procedure so it was possible the vial was not properly sealed. ZHP00406894 at ZHP00406909.

Deviation Investigation Report 18022. ZHP conducted yet another root cause investigation into the presence of NDMA. PRINSTON00088271-88281. ZHP conducted an assessment on shared equipment and ultimately "confirmed that the risk of the share equipment products is at low risk level" for cross contamination and is "still controllable." ZHP stated that according to their evaluation of residual toxicity of n-nitrosodimethylamine and the solubility of the impurity, it can be seen that the detergents purified water and ethanol used in all equipment and container can remove the impurity well." PRINSTON00088271 at PRINSTON00088279.

Deviation Investigation Report 18038. ZHP wrongly concluded that the formation of NDMA was due to "unexpected" reactions. ZHP01385193-ZHP1385273 at ZHP01385238. In the $ZnCl_2$ process, ZHP first claimed an "unexpected" reaction was the DMF's solvent impurity/degradant, dimethylamine, reacting with nitrous acid to form NDMA. ZHP01385238. However, this reaction is not unexpected and would have been recognized if a proper risk assessment was performed based on scientific analysis. The second claimed "unexpected" reaction in the TEA hydrochloride process was triethylamine's impurity/degradant, diethylamine, reacting with nitrous acid to form NDEA. ZHP01385238. However, this reaction was also not unexpected and would have been recognized if a proper risk assessment was performed. ZHP stated these events were not anticipated and they were "not in the scope of understanding at the time when we performed initial process evaluation and validation". ZHP01385193-ZHP1385273 at ZHP01385238. The reason for this was a lack of scientific rigor. Both of these reactions would have been anticipated and recognized and are well within the scope of understanding of a qualified chemist if a proper risk assessment was performed as part of the initial process evaluation and validation, or during the manufacture of the valsartan API. A proper risk assessment of the processes or identification of unidentified peaks on residual solvent GC-FID testing both independently would lead to the discovery of nitrosamine formation.

In addition, ZHP stated that NDMA and NDEA are not readily detectable when using the GC-FID method. ZHP01385238**.** This is not a valid excuse for the lack of scientific rigor in ZHP's assessment. Per FDA's cGMP guidance: "For example, investigation of an atypical impurity or

possible contaminant of a drug product or any of its components may indicate the need for additional methods or instrumentations beyond routine quality control tests. Such testing for impurities is critical to promptly and adequately evaluate the problem and protect public health." https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-requirements-laboratory-controls We should always be reminded that: The "c" in cGMP stands for "current," informing manufacturers they must always employ technologies and systems which are up to date to comply with the regulation. For ZHP to use GC-FID with lower level of detection than GC-MS, is simply inadequate and unacceptable.

Deviation Investigation Report 18043. This investigation by ZHP resulted from a facility inspection by the Italian Medicine Agency, European Medicine Agency and US Food and Drug Administration. ZHP02557594-2557671. As a result of this inspection, the FDA placed ZHP on import alert as of September 28, 2018. ZHP02557606. On September 13, 2018, the IMA issued a Statement of Non-Compliance with GMP, and noting many deviations. ZHP02557608. IMA found an "inadequate investigation of unknown peaks detected in GC-MS analysis of batches of Valsartan manufactured with the new process as optimized in July/August 2018". ZHP02557610.

QUALIFICATION OF A DRUG SUBSTANCE (API) SUPPLIER BY A FINISHED DRUG PRODUCT MANUFACTURER

Finished dose drug manufacturers validate an API manufacturer's (also referred to as a supplier) reliability by "qualifying" them. The Code of Federal Regulations calls for written procedures describing the testing of drug product components. 21 CFR 211.80. Each component must be tested for conformity with all appropriate written specifications for purity, strength, and quality. See 21 CFR 211.84(d)(2). This section provides that the manufacturer should establish "the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals." This validation allows a finished dose manufacturer to accept an API manufacturer's Certificate of Analysis instead of performing tests, aside from identity, on the API itself. The finished drug product manufacturers should test the API or validate the API supplier's reliability to ensure compliance with compendial specifications. The process of qualifying an API supplier should include an evaluation of the general manufacturing process, elements of the synthesis process, expected impurity profile and certification statements that the drug substance contains no impurities such as genotoxic carcinogens like nitrosamines. In addition to this documentation, the qualification process should include testing of API batches. This testing is done to ensure the API meets expected quality and specifications. There should be a quality agreement with the API supplier which requires the supplier to follow cGMP and describes how the finished drug product manufacturer will ensure drug substance quality including evaluation of the drug synthesis process and on-site audits of the API supplier. The quality agreement should also require notification when there are changes made to the API manufacturing process.

NOVARTIS' QUALIFICATION PROCESS DISCOVERED NDMA

It was Novartis' customer complaint in May 2018 which immediately proceeded the recall. Novartis, as a finished drug product manufacturer, seeking to purchase API discovered the presence of nitrosamines as part of its "qualification process" when conducting routine residual solvent gas chromatography testing on the ZHP API which revealed unknown peaks.

Novartis contacted ZHP regarding several unknown peaks that were present in the chromatography of the valsartan API samples. ZHP00389304-00389317; ZHP00389314. On May 22, 2018, Novartis provided ZHP with their GC method and requested a response regarding the unknown peaks. ZHP00389311. ZHP replied by providing chromatography with the a peak being identified as dimethyl sulfide and another unknown peak being identified as the "diluent of residual solvent method". ZHP00389307-389308. Novartis expressed their uncertainty over the first unknown peak being dimethyl sulfide as they use NMP as a solvent so they asked for data to support ZHP's assessment. ZHP00389307. Novartis also inquired whether identification work would be done on the other unidentified peaks to which ZHP replied that they would keep Novartis "closely updated." ZHP00389306.

Following good and accepted chemistry and pharmaceutical practices, Novartis requested Solvias conduct a further analysis to identify the peaks using gas chromatography-mass spectrometry (GC-MS) which resulted in the identification of the peak as NDMA. Solvias Report, Valsartan: Identification of unknown compounds. ZHP00190079-ZHP00190096; ZHP00190080; ZHP00400281-400298. Notably, in a June 6, 2018 email to ZHP, Novartis told ZHP that it wanted "support in understanding if the peak in the Novartis report N-Nitrosodimethylamine is possible" and also noted "[t]his peak should also be seen in the Huahai method but at an earlier retention time." ZHP00388645-00388646.

Solvias provided a tentative report that their GC tests on the API revealed one of the unknown peaks was NDMA. Solvias Report, Valsartan: Identification of unknown compounds. ZHP00190079-ZHP00190096; ZHP00190080; ZHP00400281-400298. On June 11, 2018, Kevin O'Mahony of Novartis emailed ZHP confirming that NDMA was indeed the peak after toluene in their GC analysis and their three test batches showed a quantification of approximately 200-400ppm. ZHP00388706.

Novartis and ZHP had a meeting on June 15, 2018 regarding the valsartan impurity issue, in which Novartis suggested ZHP to quickly notify the FDA of the safety issue, and also communicate the issue, in detail, to its customers. ZHP00188946-ZHP00188947. On June 15, 2018, ZHP emailed their customers stating that they "have detected a previously unknown impurity that may have genotoxic potential" and requested a temporary hold on the use of Huahai's valsartan API immediately. ZHP00399990. ZHP did not convey in this email that they identified NDMA as the impurity with "genotoxic potential" or give any of the specifics Novartis had requested. ZHP00399990.

On June 18, 2018, Prinston notified the FDA of the presence of NDMA in the Valsartan and Valsartan-HCTZ tablets. PRINSTON00000281. One month later, on July 13, 2018, ZHP through

Prinston Pharmaceutical Inc. issued a nationwide recall of Valsartan and Valsartan HCTZ tablets. PRINSTON00304075.

If finished dose manufacturers that used ZHP valsartan API which contained NDMA and NDEA in their drug products had engaged in proper ongoing supplier qualification processes including the evaluation of the ZHP API synthesis process and manufacturing changes and conducted on going risk assessments, they would have predicted the formation of and detected nitrosamines in the drug substance. Had finished dose manufacturers conducted thorough testing of the ZHP API or the finished dose drug product, they would have detected the presence of NDMA and NDEA as Novartis did. cGMP, stands for "current" good manufacturing practices which means the drug product manufacturer should use "current" and best available technologies to determine impurity profile of an API as Novartis did. Finished dose manufacturers should take these steps as they are responsible for the quality and purity of their drug product.

CONCLUSIONS AND OPINIONS

The following conclusions and opinions are expressed by me to reasonable degree of scientific certainty, and I have applied reliable, established scientific principles and methods to the facts in reaching them. These opinions are based upon the documents, literature reviewed and cited, and also upon my own professional training and experience as a chemist and in the pharmaceutical industry, including my knowledge and experience with the cited regulations.

The NDMA and NDEA present in the Valsartan containing products posed an unreasonable safety risk to patients as they are potent genotoxic, carcinogens and provide zero benefit to the patient. This is particularly important and true when patients are taking these drugs on long term or chronic basis.

The NDMA and NDEA present in the valsartan containing products occurred because of the Defendants' failure to follow current Good Manufacturing Practices. They failed to identify, analyze, evaluate, and eliminate the risk of NDMA and NDEA in valsartan containing drugs as part of their manufacturing process.

If ZHP, the API manufacturer/supplier, or the finish dose manufacturers, had conducted adequate risk assessments, the contamination of their valsartan containing drugs would have been detected and sale of the contaminated drug products would have been prevented.

The "c" in cGMP stands for "current," reminding manufacturers that they must always employ technologies and systems which are up to date in order to comply with the regulation. For ZHP and finished dose manufacturers to use GC-FID with lower level of detection than GC-MS, and not conduct further testing using GC-MS to target nitrosamines is simply unacceptable. GC-MS has been around since the mid-1980s. All of the information and technology needed to predict, detect and identify NDMA and NDEA in the valsartan containing drugs was available during the time these drugs were developed, manufactured and then sold to patients in the United States.

The Valsartan containing products that had NDMA and NDEA were adulterated (21 USC Section 351) as they were not manufactured in accordance with current good manufacturing practices as previously set forth.

The Valsartan containing products that contained NDMA and NDEA were not the same as the approved formulation and impurity profiles of Diovan or Exforge because they contained NDMA and NDEA. Thus, ZHP/Solco and the finished dose manufacturers using contaminated ZHP API sold valsartan that did not match the approved formulation of valsartan.

Generic valsartan with NDMA and/or NDEA is not chemically or pharmaceutically equivalent to the approved formulation and impurity profile of brand name RLD/Diovan (or Exforge). Pharmaceutical equivalent drug products must meet the applicable standard of identity, strength, quality and purity (See https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface), and valsartan with NDMA and NDEA does not.

EXHIBIT A

Ramin (Ron) Najafi, Ph.D.

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Alameda, CA 94501
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EXPERIENCE

Najafi Pharma Inc., dba: Emery Pharma, Alameda, CA
Founder, Chairman & CEO (2011-present)
(www.emerypharma.com)

Founded Emery Pharma as a subsidiary of NovaBay Pharmaceuticals in 2011. Established Najafi Pharma Inc. in 2015 and took Emery Pharma private in 2015 under Najafi Pharma Inc. umbrella. Established a new state-of-the art biological and chemical laboratory facility in Alameda, CA and relocated Emery Pharma there. Emery Pharma is an FDA registered and Inspected, DEA licensed, cGMP / GLP compliant. Emery Pharma focuses on pre-clinical support of early-stage biopharmaceutical companies around the globe. More on Emery Pharma at: www.emerypharma.com

NovaBay Pharmaceuticals, Inc. Emeryville, CA
Founder, Chairman & CEO (2000-2015)
(www.novabay.com)

Founded NovaBay Pharmaceuticals in December 2000 and took the company public in October of 2007. Raised a total of $100 million through public and private investment and another $100 million from non-dilutive sources such as corporate partnership with multi-national biopharmaceutical companies. Conducted multiple global clinical trials and helped establish several national and international partnerships in USA, Europe, China and Korea. Hired 50 full time pharmaceutical sales rep, and established NovaBay's Avenova as one of the fastest growing blepharitis treatment products addressing meibomian gland dysfunction.

Responsibilities:

- Took company from seed stage to clinical stage and IPO
- Recruited an experienced Board of Directors
- Assembled and Directed Senior Management Team
- Led financing efforts (Raised a total of $200 million from private, public, non-dilutive sources, nationally and internationally)
- Led efforts in Chemistry (until 2004)
- Developed Intellectual Property Base
- Led the effort in conducting multiple FDA clinical trial, USA, India, Brazil, Sri Lanka.
- Led the development of Avenova® and building a 50 person US sales force
- Led the effort in the development of Auriclosene for urology (from concept to multiple successful FDA trial)

Achievements:

- Significant partnership with China Pioneer Pharma (now the largest NovaBay investor)
- Significant partnership with Shin Poong Pharma of Seoul – S. Korea
- Significant partnership with Galderma, S.A. the world leading dermatology company (March 2009)
- Took NovaBay Public in 2007 ticker symbol: NBY listed on NYSE and TSX
- Initial Public Offering in both the United States and Canada (October 2007)
- Successfully completed financing of $15 million privately and 20 Million Publicly
- Led effort in Partnering with Alcon Laboratories, Inc. with a total deal worth ~$100 million; $10 million upfront, $15 million in annual R&D funding.
- Led effort in Partnering with Kinetic Concepts, Inc., the leading wound care company (June 2007)
- Assembled a Board of Directors with significant strength in pharmaceutical industry and experience in early, mid and late stage companies (2000-present)
- Formed Management Team with members who had significant managerial experience in major pharmaceutical companies. (2000-present)
- Helped achieve significant breakthrough stabilization of NVC-101 and NVC-422 (2000-present)
- Obtained initial US patent and filed 8 pending patents (2000-present)
- Key Publication in Peer reviewed Journal: Tetrahedron Letters 2008: Title: Remarkably Stable Chlorotaurine Derivative.

CP Lab Safety formerly known as California-Pacific Lab. Inc. Novato, CA
Founder, President and CEO (1996-2002)
(www.calpaclab.com)

Responsibilities:

- Formed company around environmental laboratory safety concept
- Obtained cost-effective manufacturing
- Built marketing, sales and distribution worldwide
- Broadened product offerings
- Developed Intellectual Property base

Achievements:

- CP Lab Safety was the recipient of the Congressional Certificate of Environmental Sustainability from Congressman Jared Huffman in recognition of the company's global effort and commitment to reducing environmental pollution (April 2016)
- Brought Manufacturing of the Ecological Funnels back to the United States (2007)
- Developed company to stage where it could be managed independently of founder
- Had several variations of initial concept developed
- Transferred manufacturing to offshore source dramatically reducing costs
- Built up direct marketing to major companies ensuring that product has regulatory mandate via US-EPA
- Established distribution through major scientific supply houses in the United States, Europe and Japan
- Built up environmental and safety catalog by adding products from third party manufacturers
- Obtained one issued and one pending patent. Obtained satisfactory six-figure settlement against copyright infringement by a major company

Applied Biosystems Division of Perkin-Elmer Corp., San Francisco
Research Scientist (1993-1996)
Responsibilities:

- Processed research and development of specialty phosphoramidites and their subsequent conversion to oligonucleotides (DNA).

Achievements:

- Developed methods for analysis of process impurities of phosphoramidites and oligonucleotides.
- Scaled up of the bench scale processes to the pilot plant.
- Invented protocols for purifying highly unstable phosphoramidites, precursors for DNA Synthesis.

- Selected as the outstanding scientist at Perkin-Elmer Applied Biosystems and the Recipient of Perkin-Elmer President's Award for Innovative Discoveries in Chemistry (September 1995).

Rhône-Poulenc Rorer Pharmaceutical, Department of Chemical Process Research and Development. Collegeville, PA
Research Scientist (1991-1993)
Responsibilities:

- Processed research and development of a series of next generation Asthma Drugs.

Achievements:

- Scaled up a hydroboration reaction from milligram to multi-kilogram quantity.
- Coordinated Process Chemistry with Pilot Plant and Analytical Group for testing and quality Control of synthesized drugs.
- Proposed and obtained approval to initiate a yearly Symposium called "Visions in Chemistry Symposium" at Rhone-Poulenc Rorer Pharmaceutical Company.
- Served as the co-chair and invited the first Symposium attendees: Professor H.C. Brown of Purdue University, recipient of 1979 Nobel Prize in Chemistry and six other well-known organoborane chemists to present at this symposium.

Aldrich Chemical Company Sheboygan Fall, WI
Senior Development Chemist (1989 - 1991).
Responsibilities:

- Led team of chemists responsible for research and development in the area of new products.

Achievements:

- Developed over 200 new products added to Aldrich catalog.
- Led a chemistry group in the area of organosilane-based reagents and synthetic intermediates.
- Conceived and designed a new version of Aldrich's patented "Oxford Sure Seal Cap" to improve its performance for highly unstable air-sensitive reagents.
- Synthesized drug candidates under Good Manufacturing Practice (GMP) protocol for use in animal / human trials.

EDUCATION

University of California, Davis; Davis, California.
Degree: Ph.D. in Organic Chemistry, December 1988.
Advisor: Professor George S. Zweifel.

University of San Francisco; San Francisco, California.
Degree: B.S. and M.S. in Organic Chemistry; June 1983.
Advisor: Professor John A. Soderquist.

TEACHING EXPERIENCE

Associate-Instructor, and **Teaching Assistant** for Advanced Organic Synthesis, Supervision of undergraduate general and organic chemistry labs. (1983 -1988)

Teaching Assistant for Organic Chemistry Laboratory, University of San Francisco, September 1982 to June 1983.

PROFESSIONAL ACTIVITIES & HONORS

-East Bay Business Journal Biotech Entrepreneur of the year 2007
-Recipient of Perkin-Elmer / Applied Biosystem President's Award for Innovative Discoveries in Chemistry (1995).
-Co-Founder of Visions in Chemistry Symposium at RPR (now Sanofi-Aventis), 1991-present
-President and Founder of Nahaal Scholarship Foundation (non-profit) (1994-2001)
-Secretary, Philadelphia Organic Chemist Club (POCC) (1993-1994)
-American Chemical Society (ACS) (1979-present)
-Sigma Xi. National Scientific Honor Society (Associate Member, 1988-present)
-Recipient of the University of California Campus-Wide Teaching Award for Outstanding Graduate Students (1988)
-Recipient of the University of California, Dow Chemical Company Graduate Teaching Assistant Award in Recognition of Outstanding Graduate Accomplishments (1987).
-Recipient of the University of San Francisco, Student Affiliates of the American Chemical Society Award for Outstanding Achievement in Chemistry (1981).

PUBLICATIONS

1. Ron Najafi, Ph.D., Neelanjan Bose, Ph.D., Eshani Nandita, Ph.D., Emery Pharma Ranitidine: FDA Citizen Petition, filed January 2, 2020 https://emerypharma.com/news/emery-pharma-ranitidine-fda-citizen-petition/

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EXHIBIT B

List of Materials Considered

- ZHP00389304
- ZHP00389314
- ZHP00683571
- Hai Wang Dep. Tr. 3/10/2021
- Hai Wang Dep. Tr.
- Minli Zhang Dep. Tr. 3/26/2021
- PRINSTON00249966, 249967
- ZHP00099424, 99441-42
- PRINSTON00075797
- TEVA-MDL2875-00042637
- Daniel Barreto Dep. Tr. Volume 1 4/14/21
- Daniel Barreto Dep. Tr. Volume 2 4/15/21
- Sushil Jaiswal Dep. Tr.
- ZHP02563814
- Reddy Neravetla Dep Tr. 05/26/21
- TORRENT-MDL2875-00366172
- TORRENT-MDL2875-00135398
- Ex. 65, Teva Dep. 230
- TEVA-MDL2875-00546489
- TEVA-MDL2875-00549883
- MYLAN-MDL2875-00705126
- PRINSTON00078386
- PRINSTON00423595
- PRINSTON00077824
- PRINSTON00075818
- PRINSTON00073120
- PRINSTON00075819
- PRINSTON00072213
- PRINSTON00071518
- PRINSTON00074772
- LP1375-PRINSTON00158177
- ZHP00063901
- ZHP02267364
- PRINSTON00073432
- PRINSTON00074773
- ZHP01793452
- ZHP01793454
- ZHP00008243
- ZHP00406066

- ZHP00190573
- ZHP01812104
- ZHP00406066
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- ZHP01859921
- ZHP00400281
- ZHP00400288
- ZHP00388706
- ZHP00198678
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- ZHP02441511
- HUAHAI-US00007585
- ZHP01748905
- ZHP02630926
- ZHP00477534
- ZHP01748916
- ZHP02118423
- ZHP02118424
- ZHP02118432
- ZHP00183574
- ZHP00331829
- ZHP00183572
- ZHP00489553
- ZHP00489548
- ZHP00389314
- ZHP00389308
- ZHP00400288
- ZHP00188946
- ZHP00399990
- PRINSTON00000281
- PRINSTON00304075
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- ZHP00406904
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- ZHP00406909
- PRINSTON00088276
- PRINSTON00088279
- ZHP01385238
- ZHP02557594

- ZHP02557606
- ZHP02557608
- ZHP02557610
- ZHP00190080
- ZHP00388645-00388646
- LP1324 - TORRENT-MDL2875-00516423
- LP476 - TORRENT-MDL2875-00365787
- LP1160 - ZHP00400281
- LP1259 - ZHP00400220
- LP1028-TORRENT-MDL2875-0000284
- LP1383 - TORRENT-MDL2875-00072650
- LP1297 - TORRENT-MDL2875-00516430
- LP1294 - TORRENT-MDL2875-00516416
- LP1296 - TORRENT-MDL2875-00516418
- LP1348 – TORRENT-MDL2875-00003958
- LP1093 - TORRENT-MDL2875-00007067
- LP1171 - TORRENT-MDL2875-00131255
- LP1163 - TORRENT-MDL2875-00004202
- LP682 - TORRENT-MDL2875-00100455
- LP1033 - TORRENT-MDL2875-00006563
- LP1109 - TORRENT-MDL2875-00504834
- LP1170 - TORRENT-MDL2875-00131251
- TEVA-MDL2875-00950663
- TEVA-MDL2875-00791611
- Min Li Dep. Tr. 4/20/21
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- PRINSTON00162407
- PRINSTON00162349
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- 20180627AIFA communication
- 20180628AIFA communication appendix
- 20180628AIFA communication
- 20180630AIFA communication
- PRINSTON000002249 (1-2 Annex-3 NDMA for TEA Process by GC-MS)

- Anthony R. Binsol Dep. Tr. 5/13/21
- Claire Lyons Dep. Tr. 4/27/21
- Elisabeth Gray Dep. Tr. 2/26/21
- Mayra Avila Dep. Tr. 5/27/21
- Michelle L. Osmian Dep. Tr. 5/6/21
- Narendra Vadsola Dep. Tr. 3/24/21
- Pan Lin Dep. Tr. 5/26/21
- Raphael Nudelman Dep. Tr. 4/8/21
- Stefan Karlsson Dep. Tr. 3/18/21
- TEVA-MDL2875-00060028 (Exhibit TEVA 0182)
- TEVA-MDL2875-00000603
- TEVA-MDL2875-00001886
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- HUAHAI-US00007581
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- PRINSTON00074760
- PRINSTON00077768
- PRINSTON00088271
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- PRINSTON00269004
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- TEVA-MDL2875-00038709
- TEVA-MDL2875-00068934
- TEVA-MDL2875-00701543
- ZHP00000417
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- ZHP01344159
- ZHP00388639